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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/909,762	07/23/2001	Roland Schule	SCH-1700 D1	2957

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EXAMINER	
MURPHY, JOSEPH F	
ART UNIT	**PAPER NUMBER**
1646	7

DATE MAILED: 07/28/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/909,762	SCHULE ET AL.	
	Examiner	Art Unit	
	Joseph F Murphy	1646	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence addr ss* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 9-14* is/are pending in the application.

4a) Of the above claim(s) *10-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9,13 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Formal Matters

Claim 8 was cancelled, claims 1 and 3-4 were amended, and new claims 13-14 were added, in Paper No. 3/31/2003. Claims 1-7, 9-14 are pending. Claims 1-7, 9, 13-14 are under consideration.

Claim Objections

Claims 1-7, 9, 13-14 are objected to because of the following informalities: They contain subject matter directed to a non-elected invention. In Paper No. 4, 10/9/2002, Applicant elected, with traverse, Group I, drawn to a method of identifying agents that regulate the transcriptional activity of human AR and SLIM3. The restriction was made final in Paper No. 5, 12/31/2002. Appropriate correction is required.

Response to Amendment and Arguments

Applicant's arguments filed 3/31/2003 have been fully considered but they are persuasive in part.

The rejections to claim 8 have been rendered moot by cancellation of the claim and are thus withdrawn.

The Objection to the Specification for improper incorporation of essential subject matter by reference to a publication is withdrawn.

The rejection of pending claims 1-7, 9 under 35 USC 112 second paragraph as being vague and indefinite in the recitation of the terms "AR", "SLIM3" and "ERB", has been obviated by Applicant's amendment, and is thus withdrawn.

Remaining issues, and new issues, are set forth below.

Claim Rejections - 35 USC § 112 first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 and 9 remain rejected, and new claim 13 is rejected, under 35 USC 112 first paragraph because the specification, while being enabling for a method of identifying agents that regulate the transcriptional activating activity of human AR and human SLIM3, does not reasonably provide enablement for a method of identifying agents that regulate the transcriptional activating activity of biologically active derivatives of human AR and biologically active derivatives of human SLIM3, nor does the specification reasonably provide enablement for a method of identifying agents that regulate the transcriptional activating activity of human AR comprising allelic modifications and human SLIM3 comprising allelic modifications. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue.

In the instant case, the claims are directed to a method of identifying agents that regulate the transcriptional activating activity of biologically active derivatives or allelic modifications of human AR and biologically active derivatives or allelic modifications of human SLIM3. Thus, the claims encompass methods using variant proteins. Applicant has only taught the method using human AR and human SLIM3 (page 16, line25 to page 17 line 5). Applicant has provided

little or no guidance to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. Applicants do not disclose any actual or prophetic examples on expected performance parameters of any of the possible derivatives or modifications of AR or SLIM3.

It is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function. For example, Voet et al. (1990) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph). It is also known in the art that a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. Thus, the amino acid sequence of a polypeptide determines

its structural and functional properties, and predictability of which amino acids can be substituted is extremely complex and well outside the realm of routine experimentation, because accurate predictions of a polypeptide's structure from mere sequence data are limited. Since detailed information regarding the structural and functional requirements of the proteins are lacking, it is unpredictable as to which derivatives or allelic modifications , if any, meet the limitations of the claims.

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives and allelic modifications recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Given the breadth of claims 1-7, 9, 13-14 in light of the predictability of the art as determined by the number of working examples, the level of skill of the artisan, and the guidance provided in the instant specification and the prior art of record, it would require undue experimentation for one of ordinary skill in the art to practice the claimed invention.

Applicant argues that one of skill in the art could readily ascertain the possible biologically active derivatives of SLIM3 that have utility in the invention. However, the methods as set forth in the instant claims merely require the presence of SLIM3, they do not require that SLIM3 has any particular activity. For instance, the methods as written do not

require the interaction of SLIM3 with the AR at all, nor do the claims require that SLIM3 has any effect on the transcriptional activity of the AR. The only requirement is that SLIM3 be present in the cell in which the method is practiced. Since SLIM3 has no function in the method, it would require undue experimentation for one of skill in the art to make derivatives or allelic modifications of SLIM3 that have activity, because no activity is set forth in the claims for SLIM3. Furthermore, even if a functional limitation for the SLIM3 variants were added, one of skill in the art would not be enabled commensurate in scope to the instant claims. Applicant argues that amino acid substitutions can be made without significantly affecting protein function, which function can be assayed (see Specification at 6-7). The instant specification, however, provides only general guidance regarding conservative amino acid substitutions and fails to provide specific guidance regarding which regions of SLIM3 are functionally important and how any given set of changes will affect that function. Thus, regardless of the fact that a functional assay is taught, there is insufficient evidence regarding how to predictably make those derivatives which would be expected to retain function. A method of finding a protein by screening is not the same as a method of making the compound.

Claim 13 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Due to the limitation of "allelic modification" recited in the claim, a determination of what the claim as a whole covers indicates that elements that are not particularly described, e.g. the sequence of the claimed allelic modifications, are encompassed by this claim. There is no actual reduction to practice of the claimed invention, or complete detailed description of the structure.

Alleles are two or more alternative forms of a gene occupying the same locus on a particular chromosome, and differing from other alleles of that locus at one or more mutational sites. In the instant case the structure of the allelic modifications are not defined. The skilled artisan cannot envision the detailed structure of the encompassed polypeptides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The amino acid sequence itself is required. Support for allelic variants is provided in the specification on page 4, line 29 to page 6, line 25, which discloses that amino acids can be substituted without significantly affecting the function of the protein. However, no disclosure, beyond the mere mention of the potential allelic modifications are made in the specification. Applicant has provided no explicit identification of any allelic modifications and no explicit identification of the structural differences between the allelic modification and the encoding reference gene sequence. This is insufficient to support the generic claims. See University of California v. Eli Lilly and Co. 43 USPQ2d at 1406. There is no known or disclosed correlation between any function and the structure of the non-described allelic modifications and the disclosed SLIM3 polypeptide. Weighing all factors in view of the level of knowledge and skill

in the art, one skilled in the art would not recognize from the disclosure that the Applicant was in possession of the claimed invention.

Claim Rejections - 35 USC § 112 second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7, 9 stand rejected for reasons of record set forth in Paper No. 5, 12/31/2002, and new claim 13 is rejected, under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite in the recitation of the term "biologically active". The term "biologically active" is not defined by the claim, and the claim gives no definition of what this activity is. Various biological activities can be attributed to a peptide. For example, "activity" could constitute transportation throughout a cell, alteration of tertiary structure due to changes in pH, ligand binding, or modulation of second messenger effect, etc. 'Activity' could also be referring to the ability of the fragment to stimulate antibody production. Claim 2-7 and 9 are rejected insofar as they depend on the recitation in claim 1of "biologically active". Applicant argues that the specification indicates what is encompassed by the use of the term. However, neither the specification nor the claims precisely define the biological activity of SLIM3, thus activities which could be considered definitive of SLIM3 are not distinguished from activities which are common to other proteins, thus the metes and bounds of the term "biologically active" cannot be determined.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-7 and 9 remain rejected, and new claim 13 is rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 5,789,170 (Chang et al.), for reasons of record set forth in Paper No. 5, 12/31/2002. U.S. Patent No. 5,789,170 has a priority date of May 23, 1996.

U.S. Patent no. 5, 789, 170 discloses the cloning and expression of a co-activator of human androgen receptor, ARA70 (column 2, lines 6-16). Based on the limitation "biologically active derivative" in claim 1, and the term "allelic modification" in claim 13, ARA 70 can be considered a biologically active derivative or allelic modification of SLIM3. U.S. Patent No. 5, 789,170 also discloses methods of screening for ligands which regulate transcriptional activity of androgen receptor in the presence of ARA70, (column 6, lines 3-15) in the yeast two-hybrid

system, using AR-GAL4 binding domain fusion constructs and ARA70-GAL4 activator domain fusion constructs (column 4, lines 23-35, see also Figure 1). Thus claims 1-7, 9, 13 are anticipated.

Applicant argues that one of skill in the art would recognize that ARA70 is not the same protein or a derivative of SLIM3. However, the claims contain no indication of any structural or functional features by which to determine whether a protein is to be considered a derivative or allelic modification of SLIM3. The claims do not present, for example, any percent identity limitation, nor any hybridization conditions for the encoding nucleotide, nor the necessity to interact with an antibody, nor any limitation wherein the derivative or allelic modification must contain a certain active site. Additionally, the claims as written do not set forth any function which the derivative or allelic modification of SLIM3 must possess, the claims only require the presence of SLIM3, or a derivative or allelic modification, in the cell in which the method is to be practiced. Thus, lacking any structural or functional indication of what is to be encompassed by the terms derivative or allelic modification of SLIM3, the claims are anticipated by the '170 patent.

While the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993), in the instant case, neither the specification nor the claims precisely define the biological activity of SLIM3, thus activities which could be considered definitive of SLIM3 are not distinguished from activities which are common to other proteins. Thus, since no clear functional limitation is set forth for the SLIM3 protein, the ARA70 protein cannot be

distinguished from the SLIM3 protein based on either structural or functional indicia, therefore the claims are anticipated by the '170 patent.

Claims 1, 3, 9, 13-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Culig et al. (1994).

Culig et al. teaches a method of measuring the effect of various compounds on the transcriptional activity of androgen receptor transfected and expressed in DU-145 cells (page 5475, Figures 1 and 2). The cells used in the method of Culig, DU-145 cells, are a prostatic tumor cell line (page 5474, column 1, second paragraph). According to the Specification, SLIM-3 is expressed in the prostate (Specification at 1, line 16). Thus, Culig et al. teaches a method of identifying agents which regulate the transcriptional activity of AR in cells expressing both AR and SLIM-3 by measuring the transcriptional activity of AR, thus claims 1, 13-14 are anticipated. The transcriptional activity of AR is indicated by measuring the transcription of CAT, thus claim 3 is anticipated. Claim 9 is anticipated because several of the agents assayed in Culig et al. function as agonists (e.g., see page 5475, Figure 1, R1881 and IGF-1).

Conclusion

No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph F. Murphy whose telephone number is 703-305-7245. The examiner can normally be reached on M-F 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on 703-308-6564. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-0294 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Joseph F. Murphy, Ph. D.
Patent Examiner
Art Unit 1646
July 11, 2003

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